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The Prognostic Accuracy of Neutrophil-Lymphocyte Ratio in COVID-19 Patients

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Abstract

Introduction: COVID-19 is a newly emerging pandemic viral disease. Multiple management guidelines were introduced; nevertheless, their efficacy is still under debate. Thus, the presences of prognostic factors are essential for predicting which patients will need more invasive treatments.

Objective: The study aims to investigate the prognostic accuracy of neutrophil-lymphocyte ratio in COVID-19 infection.

Methods: This is a prospective study done in Al-Ain Hospital in the United Arab Emirates. All the Covid-19 patients presenting to the hospital were enrolled over 1 month from 20/3 to 20/4/2020. We gathered information about their age, sex, mode of transmission, and calculated their Neutrophils/Lymphocytes ratio (NLR) from the first complete blood picture on admission. We divided the patients into two groups: those whose age was 50 years and above and the those aged less than 50 years. We chose the best NLR cut-off value based on the Youden index and receiver operating characteristic (ROC) curve analysis and the target endpoint was presence or absence of intensive care unit (ICU) admission.

Results: The study revealed that 48 patients (14%) needed ICU admission, while 296 patients (86%) were admitted to a ward or quarantine facilities. When the patient's age was > 50, and NLR was ≥ 3.10, it showed a sensitivity of 95.24% and a specificity of 92.86% for predicting the need for ICU admission. When NLR was ≥ 4.21, and the patient's age was < 50, the sensitivity and specificity were 70.3% and 93.7%, respectively.

Conclusions: NLR proved to be highly specific and sensitive in helping to identify patients who need more invasive care among people over 50 years of age with COVID-19.

Key words: Coronavirus; COVID-19; Neutrophil-Lymphocyte Ratio; Prognosis

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INTRODUCTION

Human coronaviruses (HcoVs) are an important cluster of coronaviruses (CoVs), which are linked to a spectrum of respiratory illnesses with various severities. The sensitivities may include bronchitis, pneumonia, and common cold (1). In the last 15 years, the world witnessed the appearance of 2 pathologic and zoonotic HcoVs. One was the SARS-CoV; it is a severe acute respiratory syndrome coronavirus. The second was MERS-CoV, a Middle East respiratory syndrome coronavirus (2). In the last four months, we also witnessed the new HcoV or COVID-19 as a newly emerging disease.

There are currently no approved treatments for COVID-19, although several therapeutic regimens have been applied. Of these, hydroxychloroquine, which is an anti-malarial drug, had shown to have in-vitro activity against the virus (3). Therefore, it is essential to try to explore different biomarkers to determine and evaluate the severity of patients' condition and their disposition (4).

Multiple factors were studied to evaluate their prognostic utility in COVID-19 infection for better evaluation and management, including serum amyloid A, procalcitonin, and C-reactive protein (CRP), with different results and significance (5).

Neutrophils/Lymphocytes ratio (NLR) is a marker that can be used in subclinical inflammation. It is measured by dividing neutrophil count by lymphocytes count from the peripheral blood sample (6). The NLR had a normal range between 0.78 and 3.53, according to a recent study (7). The NLR can be used as a prognostic tool in different conditions, such as predicting mortality in cardiovascular diseases, and as a prognostic marker in cancer patient (6, 8, 9).

The present study will look at the prognostic value of the NLR combined with the age in determining the need for assisted ventilation, whether invasive or not, in patients with confirmed COVID-19 infection.

Methods

Study design

This is a prospective study done in Al - Ain Hospital in UAE over one month from 20/3/2020 to 20/4/2020. During the COVID-19 pandemic, the hospital was designated as a full COVID-19 hospital, receiving and admitting patients from different areas in UAE. Consent was not obtained from patients as there was no individual information to be disclosed, while approval from the head of the department was obtained.

Study population

All the COVID-19 patients admitted to our hospital wards during the mentioned period were enrolled in the study. The patients who were discharged home were excluded from the study. We obtained the file for each patient and looked at their journey inside the hospital from the time of admission to the final disposition.

Data gathering

We gathered information about patients' age, sex, mode of transmission, and calculated their Neutrophils/Lymphocytes ratio from the first complete blood count (CBC) on admission. We divided the patients into two groups: those whose ages were 50 and above and those aged less than 50 years. We checked the NLR for each group separately. We assessed the disposition of the patients whether to intensive care unit (ICU) or the standard hospital ward/quarantine facility following the NLR combined with the age.

Statistical analysis

We calculated the specificity, sensitivity, negative and positive predictive value (NPV and PPV), the positive and negative likelihood ratio for the NLR combined with age to measure the accuracy of NLR and its prognostic accuracy. Data were recorded using a computerized statistical software, various tables carried out, and the relevant statistical test was executed. The results were analyzed and completed using receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) was calculated. A test with no better accuracy than chance has an AUC of 0.5, whereas a test with perfect accuracy has an AUC of 1. The best cut-off value of NLR was evaluated based on the Youden index. Statistical Package for Social Science (SPSS) was employed. The significance level (p-value) was determined at < 0.05 in the statistical evaluation and a confidence interval (CI) of 95 % was applied for all indicators. All the results were submitted as graphs and/or tables.

Results

Over the period of one month, 344 patients were included in this study, 283 of which were male, and 61 were female, with a male to female ratio of 3:1. The youngest patient presented was 3 months old, while the oldest patient was 83 years old, with a median of 37.2±14.4 years (Figure 1).

When inquiring about the possible mode of acquiring the infection, 145 patients (42%) had close contact with COVID-19 infected patients, 23 patients (5%) had a history of traveling to infected areas, while 176 (51%) claimed that the source of infection was unknown.

When we assessed the endpoint of disposition, we found that 48 patients (14%) needed ICU admission, while 296 patients (86%) were admitted to a ward or quarantine facility. Among

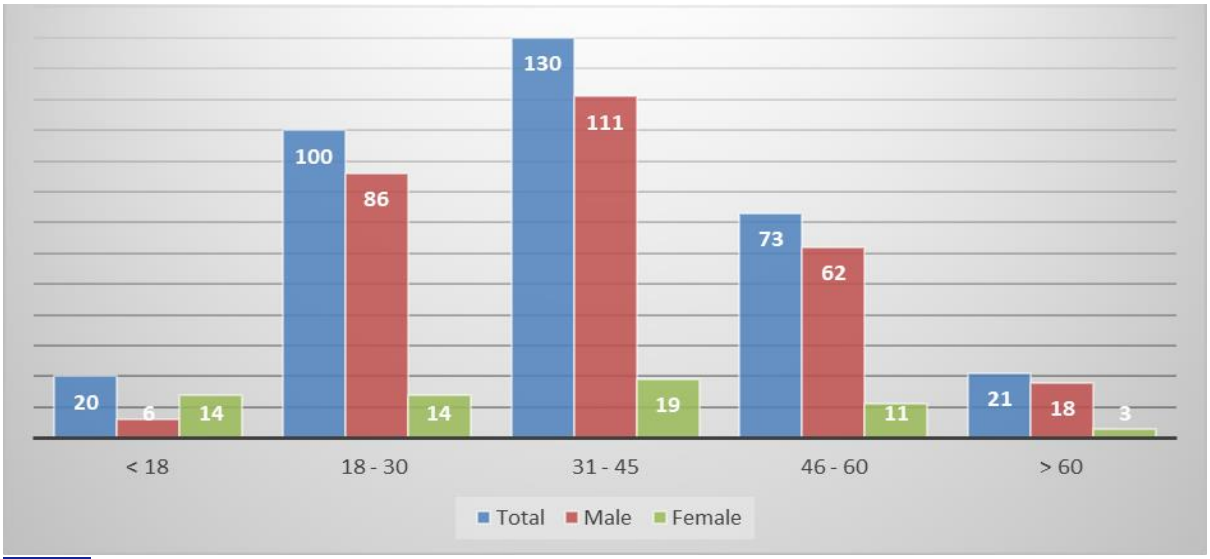

Figure 1: Age and sex distribution of the study patients

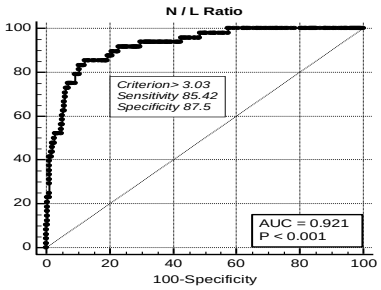

Figure 2: Receiver operating characteristic (ROC) curve of final disposition of the patients irrespective of patients' age

Table 1: The best cut-off value of NLR along with other values for all patients irrespective of their age with confidence interval of 95%

Cut-off	Sensitivity	Specificity	Likelihood ratio		Predictive value	
			+	-	+	+
			(95% CI)			
>2.75	87.50	80.41	4.47	0.16	42.00	97.54
>2.77	85.42	80.74	4.44	0.18	41.83	97.15
>3.03	**85.42**	**87.50**	**6.83**	**0.17**	**52.56**	**97.36**
>3.05	83.33	87.84	6.85	0.19	52.63	97.01
3.37	83.33	89.53	7.96	0.19	56.34	97.06

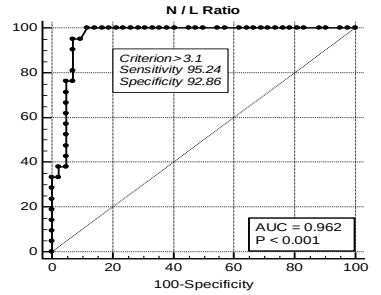

Figure 3: Receiver operating characteristic (ROC) curve of final disposition of patients when they were aged 50 years or above

Table 2: The best cut-off value of NLR along with other values for all patients irrespective of their age with confidence interval of 95%

Cut-off	Sensitivity	Specificity	Likelihood ratio		Predictive value	
			+	-	+	+
			(95% CI)			
>3	100.00	88.10	8.40	0.00	80.77	100.00
>3.05	95.24	90.48	10.00	0.053	83.33	97.43
>3.1	**95.24**	**92.86**	**13.33**	**0.051**	**87**	**97.5**
>4	76.19	92.86	10.67	0.26	84.21	88.63
>4.14	76.19	95.24	16.00	0.25	88.89	88.89

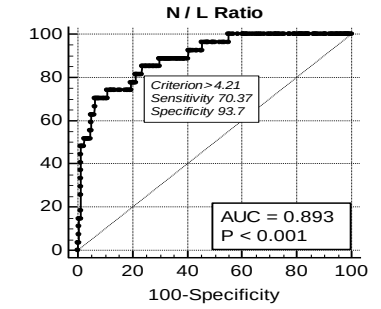

Figure 4: Neutrophils/Lymphocytes ratio (NLR) when the patients' age is less than 50 years

Table 3: The best-cut off value of Neutrophils/Lymphocytes ratio (NLR) along with other values for patients aged < 50 years with confidence interval of 95%.

Cut-off	Sensitivity	Specificity	Likelihood ratio		Predictive value	
			+	-	+	+
			(95% CI)			
>3.37	74.07	88.98	6.72	0.29	41.64	96.99
>3.43	70.37	88.98	6.38	0.33	40.40	96.58
>4.21	**70.37**	**93.70**	**11.17**	**0.32**	**54.25**	**96.73**
>4.23	66.67	93.70	10.58	0.36	52.91	96.36
>4.38	62.96	94.09	10.66	0.39	53.08	95.98

patients who were admitted to the ICU, nine patients (18.75%) died. When we evaluated the connection of ICU admission with the patients' age group, we found that 21 patients (43.75%) were 50 years of age or older and among them, 4 patients (19 %) died. Plus, 27 patients (56.25 %) were aged less than 50 years and 5 patients (18.51 %) died among them.

When we assessed the correlation between NLR and death among all of the patients, irrespective of their age, the AUC was 0.917 and the P-value was < 0.0001. The Youden index pointed out that the best cut-off value of NLR was > 4.21. It had a sensitivity of (88.89%) and specificity of (86.87%), a positive predictive value of (15.38%) and, a negative predictive value of (99.65%). In addition, the positive likelihood ratio was (6.77), and the negative likelihood ratio was (0.13).

When we assessed the NLR among all of the patients, irrespective of their age, the AUC was 0.921 and the P-value was < 0.001. The Youden index pointed out that the best cut-off value of NLR was > 3.03. The study found that 80 patients (23%) had NLR ≥ 3.03, while 264 patients (77%) had NLR < 3.03. It had a sensitivity of (85.42%) and specificity of (87.5%) (Figure 2 and Table 1).

The study revealed that 63 patients (21.6%) were aged 50 years or above, while 281 patients (81.6%) were aged less than 50 years.

We then did a high sensitivity analysis to assess the NLR in combination with age and checked patients' disposition. For patients whose were aged 50 years or above, the best cut off value of NLR was > 3.10 based on the Youden index and ROC analysis. It had a high sensitivity (95.24%) and specificity (92.8%) for predicting the need for ICU admission. Also, we found that it had a positive predictive value of 87% and a negative predictive value of 97.5%. In addition, the positive likelihood ratio was (13.33), and the negative likelihood ratio was (0.051). All these values were reported with a confidence interval of 95 % and P-value < 0.001 (Figure 3 and Table 2).

For patients, who were aged less than 50 years, the best cut-off value of NLR was > 4.21 based on the Youden index and ROC analysis. It had a sensitivity of (70.37%) and specificity of (93.70%) for predicting the need for ICU admission. Also, we found that it had a positive predictive value of (54.25%) and a negative predictive value of (96.73%). In addition, the positive likelihood ratio was (11.17), and the negative likelihood ratio was (0.32). All these values were reported with a confidence interval of 95 % and a P-value < 0.001 (Figure 4 and Table 3).

Discussion

The above-mentioned results indicated that when the NLR was ≥ 3.03 for the general population, irrespective of the patients' age, it had acceptable sensitivity and specificity of 85% and 87%, respectively.

This questions its capability as an accurate screening or ruling out tool. However, if we combined NLR with the age of 50 or above, the sensitivity and specificity markedly increased. Indeed, the high sensitivity of this ratio in patients who are aged 50 years or above makes it a quick and simple tool with excellent efficacy for screening patients who need more attention and careful evaluation due to their high vulnerability to respiratory deterioration. Additionally, the high specificity of this ratio, in combination with age, gave it an additional privilege of ruling out the low-risk patients. This is also reinforced by the elevated positive likelihood ratio, along with the exceptionally low negative likelihood ratio. Our study results are supported by two more studies that backed up the prognostic utility of NLR in COVID-19 patients despite the small number of patients enrolled in the two studies (10, 11).

When we looked at the NLR of patients who were aged less 50 years, we found that sensitivity is average, which decreases its privilege as a screening tool. However, its specificity was good and could be used as ruling out gadget of low-risk patients. This is supported by high negative predictive value and low negative likelihood ratio.

The study revealed that most of the patients were male with clear evidence that the infection is more prevalent and severe in male patients. This may be due to a working environment that is mostly made up of men or due to the negligence men in maintaining social distance and taking precautions. These results were similar to other studies in China and the USA (12, 13).

The study showed that travel history was the least frequent cause of acquiring the disease, and this was attributed to the lockdown of the country. In addition, a large percentage did not know the source of their infection and this demonstrated the spread of infection in the community, and hence, social distancing and taking precautions are essential steps to prevent infection.

Limitations

The lack of sufficient recourses on this topic meant that we could not read more about it and compare due to the novelty of this disease. In addition, there were limited international peer-reviewed articles on this issue we could compare our results with, and the value of NLR was not generally agreed upon.

Conclusions

NLR proved to be highly specific and sensitive in identifying those who needed more invasive care among COVID-19 patients aged 50 years or more. Hence, patients with higher initial NLR should receive more attention due to the high possibility of deteriorating and needing intensive care unit admission in their journey of care.

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Authors' contribution

ME: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration. MA-K: Methodology, Software, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization. WR: Investigation, Data Curation. HJK: Software, Investigation, Data Curation.

CONFLICT OF INTEREST
None declared.

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